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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/801,196	03/06/2001	Kai Wang	60117-61	4095

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EXAMINER	
SITTON, JEHANNE SOUAYA	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 09/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/801,196	WANG ET AL.	
	Examiner	Art Unit	
	Jehanne S. Sitton	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-7 and 25-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-7, and 25-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4)☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: _____.

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DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 4/4/2005 has been entered.

2. Currently, claims 1, 3-7 and 25-29 are pending in the instant application. All the amendments and arguments have been thoroughly reviewed but are deemed insufficient to place this application in condition for allowance. The following rejections constitute the complete set being presently applied to the instant Application.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

New Grounds of Rejection

Claim Rejections - 35 USC § 101

4. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

5. Claims 1, 3-7, and 25-29 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility.

Claims 1, 3-7, and 25-29 are not supported by a specific or substantial utility for the following reasons. The specification asserts that nucleic acids of SEQ ID NOS 1, 3, and 5 can be used to express proteins (page 6) or to make probes and primers to detect SEQ ID NOS 1, 3, and 5 (page 4, last para), however these are non specific uses that would be applicable to any nucleic acid sequence, and does not set forth a specific use for the claimed nucleic acids. The specification further asserts that SEQ ID NOS 1, 3, and 5 could be used to encode proteins wherein inhibition of such would be used to reduce hair growth (see p. 9). The claims lack substantial utility, however, because further experimentation would be required to reasonably confirm such use. The specification cites Styczynski et al (US Patent 5,962,466) as teaching a method of inhibiting hair growth by inhibiting matrix metalloproteases. However, Styczynski et al only teach inhibiting MMP2 and MMP 9 collagenase activity, whereas MMP 2 and MMP 9 only showed 31.6 and 23.2% identity to the protein encoded by SEQ ID NO 5. The protein encoded by SEQ ID NO: 5, however, showed higher homology (about 46% identity) to the stromylin family of matrix metalloproteases, which have different functions that that of collegenases.

While SEQ ID NO 5 appears to belong to the family of Matrix Metalloproteases, this family comprises a large group of proteins that are involved in the degradation of the extracellular matrix (see Yang and Kurkinen, J. BC, 1998; vol. 273, p 17893, col 1). While the members of this large family of proteins share some similar domains, the members of the family have distinct structures and function, and have wide and often overlapping substrate specificities

depending on the group they are in. These groups include collagenases, gelatinases, stromelysins, and membrane-type MMPs. However, as noted, this large group of proteins have different biological functions. Nagase teaches (Nagase and Woessner, J. BC, vol. 274, pp 21491-21494; 1999) that MMPs participate in many normal biological processes such as embryonic development, organ morphogenesis, nerve growth, apoptosis, etc (see p. 21493, col. 1 "Biological and Pathological Roles of Matrixins"). Nagase teaches that while the main function of matrixins is removal of the extracellular matrix during tissue resorption and progression of many diseases, MMPs also alter biological functions of extracellular matrix macromolecules by specific proteolysis. Nagase teaches that MMP-2 cleaves the Ala586-Leu587 bond in laminin and induces the migration of normal breast epithelial cells. In contrast, cleavage of type I collagen by MMP-1 and MMP-13 initiates keratinocyte migration during reepithelialization and osteoclast activation. Fig 1 of Nagase illustrates the structural similarities and differences between known matrix metalloproteases. The degree of % identity of SEQ ID NO 5 to stromelysins does not indicate a particular biological function or activity for SEQ ID NOS 1, 3, or 5, as the art teaches that stromelysins do not necessarily have the same activity. For example, Luo et al (JBC, vol. 277, pp 25527-25536, 2002) teaches that unlike most MMPs, ST3 (MMP 11) is characterized by a distinct substrate specificity and a specific regulation and is not directly involved in extracellular matrix degradation (see abstract). Bodey et al (In Vivo, vol. 15, 2001, abstract) teach that MMP3, and MMP10, corresponding to stromelysins 1 and 2, share 82% sequence homology but exhibit difference in cellular synthesis and inducibility by cytokines and growth factors in vitro (see abstract). Further, Kerkela et al (British Journal of Cancer, vol. 84, 2001, abstract) teaches that expression of stromelysin 1 (MMP 3) has been shown to correlate

with tumor invasiveness in skin tumors, but that stromelysin 2 (MMP 10) expression did not. Therefore, the art does not support a predictable correlation between the structure of stromelysins and their functions and further, as illustrated by the teachings in the art, there is no predictable correlation as to the function and specificity of a particular polypeptide based on domain/homology analysis to known MMPs or more particularly, the class of stromelysins.

Given the teachings of the art as set forth above, that is that matrix metalloproteases, while containing some similar domains, have different activities, the skilled artisan would not be able to predictably correlate that inhibition of the polypeptide encoded by SEQ ID NO 5 would result in reducing hair growth based solely on the degree of % identity exhibited by the protein to various other MMPs, particularly MMP's which exhibit only 31.6% (MMP-2) and 23.2% (MMP-9) identity. Berendsen (Science, vol 282, 1998, pages 642-643) teaches that when homology analysis between amino acid sequences in databases drops below 25%, the reliability of database originated methods [to assess structure/function] drops to nearly zero (page 642, 2nd col). Additionally, the art does not support that alignment methods such as BLAST can predictably establish the function or biological activity of an unknown protein. For example, Fetrow teaches (Fetrow et al., J. Mol. Biol., vol. 282, pp 703-711, 1998) that although function prediction by homology to previously characterized proteins is extremely successful and is fast, cheap and reliable, there are several problems that limit its potential utility, one of which is that sequence homology does not guarantee functional similarity (p 704, col. 1, 1st full paragraph). Fetrow teaches that "threading"(analysis using structure prediction tools) can identify topological cousins, that is, protein families such as the α/β barrels with similar structures, but dissimilar functions. Fetrow teaches using a three dimensional descriptor of the active site of a protein,

termed "fuzzy functional form" (FFF) and argues that threading alone is not enough to provide the required information about function because it has been shown that pairs of proteins can have similar structures but unrelated functions (p. 706, col. 2, last para). Fetrow teaches that because such topological cousins exist, knowledge of the structure is not equivalent to identification of protein function. Skolnick (Skolnick and Fetrow, TIBTECH, January 2000, vol. 18, pp 34-39) teaches (p. 35, "Box 1") that a common protein characteristic that makes functional analysis based only on homology especially difficult is the tendency of proteins to be multifunctional. Skolnick teaches that for example, lactate dehydrogenase binds NAD, substrate, and zinc and performs a redox reaction and that each of these occurs at different functional sites that are in close proximity and the combination of all four sites creates the fully functional proteins. Skolnick also cites RecA which contains a DNA binding domain, a multimerization domain and additional sites that bind regulatory proteins. Skolnick also teaches that the serine threonine phosphatase superfamily is a prime example of the difficulties of using standard sequence analysis to recognize the multiple functions found in single proteins. Skolnick teaches that this large protein family is divided into a number of subfamilies, all of which contain an essential phosphatase active site. He teaches that subfamilies 1, 2A and 2b exhibit 40% or more sequence identity between them, however each of these subfamilies is apparently regulated differently by the cell and observation suggest that there are different functional sites at which regulation can occur. Skolnick teaches that because the sequence identity between subfamilies is so high, standard sequence similarity methods could easily misclassify new sequences as members of the wrong subfamily if the functional sites are not carefully considered.

Therefore, although the alignment studies provided by the specification indicate that the claimed polypeptide contains zinc binding domains, a hemopexin domain, and a cystein switch domain, and that the claimed polypeptide likely belongs to the matrix metalloprotease family, such alignment is not sufficient to indicate to the skilled artisan the specific function or biological activity of the claimed polypeptides, so that the artisan would know how to use the claimed invention. The art with regard to sequence homology specifically teaches that sequence alignment alone does not necessarily provide a predictable correlation between the structure and specific function of a protein. The art with regard to matrix metalloproteases, as cited above, demonstrates that alignment methods with SEQ ID NO: 6 provide a variety of different proteins that have different biological functions and specificities, any of which SEQ ID NO: 6 may share. The specification, however, has not taught the actual activity or specificity of SEQ ID NO: 6, therefore it is unclear which of these functions and specificities SEQ ID NO: 6 would be predictably associated with.

In *Brenner v. Manson*, 148 U.S.P.Q. 689 (1966), a novel compound which was structurally analogous to other compounds which were known to possess anti-tumor activity was alleged to be potentially useful as an anti-tumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 U.S.C. §101, which requires that an invention must have either an immediately apparent or fully disclosed "real world" utility. The court held that:

> The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial

> utility. . . . [u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field. . . . a patent is not a hunting license. . . .[i]t is not a reward for the search, but compensation for its successful conclusion.

The instant claims are drawn to nucleic acids encoding proteins which has no identified activity. The function of this gene and its resulting protein are as yet undetermined with no known function or biological significance. Until some actual and specific significance can be attributed to the protein identified in the specification, or the gene encoding it, one of skill in the art would be required to perform additional experimentation in order to determine how to use the claimed invention. As the claimed sequences have no specific or substantial utility, nor does the protein MMP-25, encoded by the claimed nucleic acids, methods of using such nucleic acids to identify a "MMP-25" polypeptide also lack a specific and substantial utility for the reasons set forth above.

Claim Rejections - 35 USC § 112

6. Claims 1, 3-7 and 25-29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Additionally, since the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

The claims are broadly drawn to nucleic acids that consist of SEQ ID NO 1 or comprise a nucleotide sequence "set forth in SEQ ID NO 5" (amended claim 1), or encode a polypeptide comprising "an amino acid sequence as set forth in SEQ ID NO: 4 or 6", nucleic acid sequences comprising SEQ ID NO: 3 or 5, or the complement thereof, as well as sequences that encode SEQ ID NO: 4 or 6. The claims are also drawn to a method of detecting a nucleic acid encoding all or part of MMP-25 by detecting hybridization with oligonucleotides encoding a peptide consisting of amino acids 1-61, 98-111 or 161-170 of SEQ ID NO: 6.

The recitation in claims 1, 27, and 28 encompasses mutants, variants, and homologs of SEQ ID NOS 1, 3, and 5, from any source. However, the specification does not provide enough guidance to the skilled artisan to make or use sequences commensurate in scope with the broadly claimed invention (claims 1, 3-7 and 25-29).

The specification teaches that SEQ ID NO 5 encodes a matrix metalloprotease that has the highest % identity to the stromelysin family of matrix metalloproteases (46%). The specification teaches that SEQ ID NO 3 encodes a splice variant of SEQ ID NO 5,which lacks a Zn binding domain. The specification teaches that SEQ ID NO 1 encodes a fragment of SEQ ID NO 5, and SEQ ID NO 3. The specification teaches that the claims encompass variants that retain structural and functional characteristics more similar to MMP 25 (polypeptide encoded by SEQ ID NO 5) than to non type MMP 25 polypeptides. However, the specification does not teach the specific biological activity or function of SEQ ID NOS 3 or 5, such that the skilled artisan could predictably determine whether a nucleic acid encoded a matrix metalloprotease or MMP 25, based solely on it's nucleic acid sequence or it's ability to hybridize to parts of SEQ ID NO 5 or sequences which encoded parts of SEQ ID NO: 6. .

While SEQ ID NO 5 appears to belong to the family of Matrix Metalloproteases, Matrix Metalloproteases comprise a large group of proteins that are involved in the degradation of the extracellular matrix (see Yang and Kurkinen, J. BC, 1998; vol. 273, p 17893, col 1). This large group of proteins share similar domains with distinct structure and function, and have wide and often overlapping substrate specificities depending on the group they are in. These groups include collagenases, gelatinases, stromelysins, and membrane-type MMPs. However, this large group of proteins have different biological functions. Nagase teaches (Nagase and Woessner, J. BC, vol. 274, pp 21491-21494; 1999) that MMPs participate in many normal biological processes such as embryonic development, organ morphogenesis, nerve growth, apoptosis, etc (see p. 21493, col. 1 "Biological and Pathological Roles of Matrixins"). Nagase teaches that while the main function of matrixins is removal of the extracellular matrix during tissue resorption and progression of many diseases, MMPs also alter biological functions of extracellular matrix macromolecules by specific proteolysis. Nagase teaches that MMP-2 cleaves the Ala586-Leu587 bond in laminin and induces the migration of normal breast epithelial cells. In contrast, cleavage of type I collagen by MMP-1 and MMP-13 initiates keratinocyte migration during reepithelialization and osteoclast activation. Fig 1 of Nagase illustrates the structural similarities and differences between known matrix metalloproteases. The degree of % identity of SEQ ID NO 5 to stromelysins does not indicate a particular biological function or activity for SEQ ID NOS 1, 3, or 5, as the art teaches that stromelysins do not necessarily have the same activity. For example, Luo et al (JBC, vol. 277, pp 25527-25536, 2002) teaches that unlike most MMPs, ST3 (MMP 11) is characterized by a distinct substrate specificity and a specific regulation and is not directly involved in extracellular matrix degradation (see abstract).

Bodey et al (In Vivo, vol. 15, 2001, abstract) teach that MMP3, and MMP10, corresponding to stromelysins 1 and 2, share 82% sequence homology but exhibit difference in cellular synthesis and inducibility by cytokines and growth factors in vitro (see abstract). Further, Kerkela et al (British Journal of Cancer, vol. 84, 2001, abstract) teaches that expression of stromelysin 1 (MMP 3) has been shown to correlate with tumor invasiveness in skin tumors, but that stromelysin 2 (MMP 10) expression did not. Therefore, the art does not support a predictable correlation between the structure of stromelysins and their functions and further, as illustrated by the teachings in the art, there is no predictable correlation as to the function and specificity of a particular polypeptide based on domain/homology analysis to known MMPs or more particularly, the class of stromelysins..

Further, with regard to SEQ ID NO 3 which encodes a protein lacking a key domain that is conserved among MMPs, and SEQ ID NO 1, which encodes only a fragment of a putative MMP, neither the specification nor the art teach a function for such sequences, and therefore, the skilled artisan would be unable to determine whether a nucleic acid sequence belonged to the claimed genus of nucleic acids, other than by SEQ ID NO, nor how to use a nucleic with the sequence of SEQ ID NO: 1 or comprising SEQ ID NO: 3.

The specification further does not enable a use for the claimed sequences. The specification asserts that nucleic acids of SEQ ID NOS 1, 3, and 5 can be used to express proteins or make probes and primers to detect SEQ ID NOS 1, 3, and 5, however these are non specific uses that would be applicable to any nucleic acid sequence, and does not set forth a specific use for the claimed nucleic acids. The specification further asserts that SEQ ID NOS 1, 3, and 5 could be used to encode proteins wherein inhibition of such would be used to reduce

hair growth (see p. 9). The specification cites Styczynski et al (US Patent 5,962,466) as teaching a method of inhibiting hair growth by inhibiting matrix metalloproteases. However, Styczynski et al only teach inhibiting MMP2 and MMP 9 collagenase activity, whereas MMP 2 and MMP 9 only showed 31.6 and 23.2% identity to the protein encoded by SEQ ID NO 5, which is far less than the % identity that the protein encoded by SEQ ID NO 5 exhibited with stromelysins. Given the teachings of the art as set forth above, that is that matrix metalloproteases, while containing similar domains, have different activities, the skilled artisan would not be able to predictably correlate that inhibition of the polypeptide encoded by SEQ ID NO 5 would result in reducing hair growth based solely on the degree of % identity exhibited by the protein to various other MMPs. Additionally, the art does not support that alignment methods such as BLAST can predictably establish the function or biological activity of an unknown protein. For example, Fetrow teaches (Fetrow et al., J. Mol. Biol., vol. 282, pp 703-711, 1998) that although function prediction by homology to previously characterized proteins is extremely successful and is fast, cheap and reliable, there are several problems that limit its potential utility, one of which is that sequence homology does not guarantee functional similarity (p 704, col. 1, 1st full paragraph). Fetrow teaches that "threading"(analysis using structure prediction tools) can identify topological cousins, that is, protein families such as the α/β barrels with similar structures, but dissimilar functions. Fetrow teaches using a three dimensional descriptor of the active site of a protein, termed "fuzzy functional form" (FFF) and argues that threading alone is not enough to provide the required information about function because it has been shown that pairs of proteins can have similar structures but unrelated functions (p. 706, col. 2, last para). Fetrow teaches that because such topological cousins exist, knowledge of the structure is not equivalent to identification of

protein function. Skolnick (Skolnick and Fetrow, TIBTECH, January 2000, vol. 18, pp 34-39) teaches (p. 35, "Box 1") that a common protein characteristic that makes functional analysis based only on homology especially difficult is the tendency of proteins to be multifunctional. Skolnick teaches that for example, lactate dehydrogenase binds NAD, substrate, and zinc and performs a redox reaction and that each of these occurs at different functional sites that are in close proximity and the combination of all four sites creates the fully functional proteins. Skolnick also cites RecA which contains a DNA binding domain, a multimerization domain and additional sites that bind regulatory proteins. Skolnick also teaches that the serine threonine phosphatase superfamily is a prime example of the difficulties of using standard sequence analysis to recognize the multiple functions found in single proteins. Skolnick teaches that this large protein family is divided into a number of subfamilies, all of which contain an essential phosphatase active site. He teaches that subfamilies 1, 2A and 2b exhibit 40% or more sequence identity between them, however each of these subfamilies is apparently regulated differently by the cell and observation suggest that there are different functional sites at which regulation can occur. Skolnick teaches that because the sequence identity between subfamilies is so high, standard sequence similarity methods could easily misclassify new sequences as members of the wrong subfamily if the functional sites are not carefully considered. Therefore, although the alignment studies provided by the specification indicate that the claimed polypeptide contains zinc binding domains a hemopexin domain and a cystein switch domain, and that the claimed polypeptide likely belongs to the matrix metalloprotease family, such alignment is not sufficient to indicate to the skilled artisan the specific function or biological activity of the claimed polypeptides, so that the artisan would know how to use the claimed invention. The art with

regard to sequence homology specifically teaches that sequence alignment alone does not necessarily provide a predictable correlation between the structure and specific function of a protein. The art with regard to matrix metalloproteases, as cited above, demonstrates that alignment methods with SEQ ID NO: 6 provide a variety of different proteins that have different biological functions and specificities, any of which SEQ ID NO: 6 may share. The specification, however, has not taught the actual activity or specificity of SEQ ID NO: 6, therefore it is unclear which of these functions and specificities SEQ ID NO: 6 would be predictably associated with.

To practice the invention as broadly as it is claimed, the skilled artisan would be required to first determine the substrate specificity and biological activity and function for the polypeptide encoded by SEQ ID NO 5 (SEQ ID NO: 6) and then determine if any of the polypeptides encoded by SEQ ID NOS 1 or 3 possessed the same. The skilled artisan would then be required to mutate every position to determine which amino acids could be changed but still result in a polypeptide with the same function. Additionally claim 3 requires hybridization at unspecified conditions to nucleic acids that encode sequences within SEQ ID NO: 6 wherein hybridization identifies all or a part of an MMP-25 polypeptide. Such recitation encompass a method of detecting any variant, mutant, or homolog nucleic acid sequence of SEQ ID NO: 5, and designating it an "MMP-25" based solely on the fact that it would contain a sequence that would hybridize under unspecified conditions to nucleic acids that encode sequences within SEQ ID NO: 6. However, the specification has provided no predictable correlation that a sequence's ability to hybridize to nucleic acids encoding regions within SEQ ID NO: 6 would render it an "MMP-25" sequence. Further, the specification broadly defines "MMP-25" as including any polypeptide or nucleic acid of the MMP family and having at least 50% up to 95% amino acid

identity to SEQ ID NO: 6". It is clear however, that many sequences would be able to hybridize to a nucleic acid encoding regions of SEQ ID NO: 6 that would not belong in the MMP family let alone be designated an MMP-25. As the specification does not teach the function of SEQ ID NO: 6, the skilled artisan would be required to first determine the activity of SEQ ID NO: 6 (MMP-25) and then would be required to screen each polypeptide encoded by a sequence which was able to hybridize to nucleic acids within SEQ ID NO: 6, to determine which of these sequences was an "MMP-25" polypeptide. As neither the specification nor the art teach a function for the polypeptide encoded by SEQ ID NO 5, let alone that for SEQ ID NOS 1 and 3, the skilled artisan would be required to perform a large amount of trial and error analysis, the results of which are unpredictable given the lack of guidance in the specification and the teachings of unpredictability in the art, to practice the invention as broadly as it is claimed. Such experimentation is considered undue.

Response to Arguments

7. No arguments have been presented in the response. The rejection is maintained for the reasons made in the previous office actions and reiterated above.

Written Description

8. Claims 1, 5-7 and 28-29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn to nucleic acids that comprise "a nucleotide sequence as set forth in SEQ ID NOS 5", nucleic acid sequence encoding a polypeptide "comprising an amino acid sequence as set forth in SEQ ID NOS 4 and 6". Such recitation encompasses sequences that can comprise any fragment from within SEQ ID NO: 3 and 5, and includes a vary large genus of mutants, variants, and homologs of SEQ ID NOS 3 and 5, from any source, as well as unrelated sequences, including genomic sequences. As the specification does not teach or describe the activity of SEQ ID NO: 6, the claims encompass unknown functional variants and homologs of SEQ ID NO 6, from any source, that have neither been taught or described by the specification.

The specification teaches that SEQ ID NO 5 encodes a matrix metalloprotease that has the highest % identity to the stromelysin family of matrix metalloproteases (46%). The specification teaches that SEQ ID NO 3 encodes a splice variant of SEQ ID NO 5,which lacks a Zn binding domain. The specification teaches that SEQ ID NO 1 encodes a fragment of SEQ ID NO 5, and SEQ ID NO 3. The specification teaches that the claims encompass variants that retain structural and functional characteristics more similar to MMP 25 (polypeptide encoded by SEQ ID NO 5) than to non type MMP 25 polypeptides. However, the specification does not teach the specific biological activity or function of SEQ ID NOS 3 or 5, such that the skilled artisan could determine whether a nucleic acid encoded a polypeptide belonging to such a large genus of polypeptides based solely on possession of a few nucleic acids in common with SEQ ID NO: 3 or 5, or based on having a certain percent amino acid sequence or nucleic acid sequence identity with SEQ ID NOS 6 or 5, respectively. The disclosure of the sequence of SEQ ID NOS 1, a fragment, 3, a splice variant, and 5, a full length nucleic acid sequence, is not representative

of the large genus of mutants, functional variants and homologs of SEQ ID NO: 6, from any source.

While SEQ ID NO 5 appears to belong to the family of Matrix Metalloproteases, Matrix Metalloproteases comprise a large group of proteins that are involved in the degradation of the extracellular matrix (see Yang and Kurkinen, J. BC, 1998; vol. 273, p 17893, col 1). This large group of proteins share similar domains with distinct structure and function, and have wide and often overlapping substrate specificities depending on the group they are in. These groups include collagenases, gelatinases, stromelysins, and membrane-type MMPs. However, this large group of proteins have different biological functions. Nagase teaches (Nagase and Woessner, J. BC, vol. 274, pp 21491-21494; 1999) that MMPs participate in many normal biological processes such as embryonic development, organ morphogenesis, nerve growth, apoptosis, etc (see p. 21493, col. 1 "Biological and Pathological Roles of Matrixins"). Nagase teaches that while the main function of matrixins is removal of the extracellular matrix during tissue resorption and progression of many diseases, MMPs also alter biological functions of extracellular matrix macromolecules by specific proteolysis. Nagase teaches that MMP-2 cleaves the Ala586-Leu587 bond in laminin and induces the migration of normal breast epithelial cells. In contrast, cleavage of type I collagen by MMP-1 and MMP-13 initiates keratinocyte migration during reepithelialization and osteoclast activation. Fig 1 of Nagase illustrates the structural similarities and differences between known matrix metalloproteases. Further, the degree of % identity of SEQ ID NO 5 to stromelysins does not indicate a particular biological function or activity for SEQ ID NOS 1, 3, or 5, or functional fragments of such, as the art teaches that stromelysins do not necessarily have the same activity. For example, Luo et al (JBC, vol.

277, pp 25527-25536, 2002) teaches that unlike most MMPs, ST3 (MMP 11) is characterized by a distinct substrate specificity and a specific regulation and is not directly involved in extracellular matrix degradation (see abstract). Bodey et al (In Vivo, vol. 15, 2001, abstract) teach that MMP3, and MMP10, corresponding to stromelysins 1 and 2, share 82% sequence homology but exhibit difference in cellular synthesis and inducibility by cytokines and growth factors in vitro (see abstract). Further, Kerkela et al (British Journal of Cancer, vol. 84, 2001, abstract) teaches that while expression of stromelysin 1 (MMP 3) has been shown to correlate with tumor invasiveness in skin tumors, but that stromelysin 2 (MMP 10) expression did not. Therefore, the art does not support a predictable correlation between the structure of stromelysins and their functions. Further, with regard to SEQ ID NO 3 which encodes a protein lacking a key domain that is conserved among MMPs, and SEQ ID NO 1, which encodes only a fragment of a putative MMP, neither the specification nor the art teach a function for such, and therefore, the skilled artisan would be unable to determine whether a nucleic acid sequence belonged to the claimed genus of nucleic acids, other than by SEQ ID NO.

The claims encompass an extremely large genus of nucleic acids, such that the recitation of SEQ ID NO 3 or 5, or the partial fragment of SEQ ID NO 1 does not provide a teaching of a substantial portion of the claimed genus of mutants, variants, or homologs, or genomic sequences corresponding to such, from any source. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification

does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

With the exception of SEQ ID NOS: 1, 3, and 5, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides and/or proteins, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993), and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.

It is noted that as the nucleic acid sequences of claims 1, and 28-29 lack sufficient written description, claims drawn to complementary sequences, and vectors and host cells comprising such sequences also lack sufficient written description.

Response to Arguments

9. No arguments have been presented in the response. The rejection is maintained for the reasons made in the previous office actions and reiterated above. This rejection can be overcome by reciting in claim 1: "comprising the nucleotide sequence set forth in SEQ ID NO: 5", and in claims 28 and 29, "comprising the amino acid sequence set forth in SEQ ID NO: 4 [6]" respectively.

Claim Rejections - 35 USC § 102

10. Claims 1, 28 and 29 are rejected under 35 U.S.C. 102(b) as being anticipated by Accession number AA424347 (Oct. 1997).

Accession number AA424347 teaches a sequence which is identical to positions 653-1063 of SEQ ID NO 3, and positions 741-1151 of SEQ ID NO 5, therefore the accession number teaches a nucleic acid molecule that comprises "a" nucleotide sequence as set forth in" SEQ ID NO: 5. As SEQ ID NOS 3 and 5 encode the polypeptides of SEQ ID NOS 4 and 6, respectively, the Accession number further teaches a nucleic acid which encodes a polypeptide comprising "*an* amino acid sequence set forth in" SEQ ID NO: 4 or 6. The claims are not limited to sequences that comprise the [full length] sequence of SEQ ID NOS 5, or the nucleic acids encoding the full length of SEQ ID NOS 4 or 6.

11. Claims 1, 3, and 28, and 29 are rejected under 35 U.S.C. 102(b) as being anticipated by Brennan (US Patent 5,474,796).

Brennan teaches making an array of all possible isolated 10 mer nucleic acid sequences. The recitation of "a nucleotide sequence..." encompasses fragment sequences within the cited SEQ ID NOS, which are taught by Brennan. Brennan further teaches hybridizing the array of all possible 10 mers to a sample containing target nucleic acid (col. 3, lines 10-22; col. 9, line 48-col 10). With regard to claim 3, the recitation of "encoding a peptide that consists of an amino acid sequence selected from the group consisting of *amino acids* at *positions* ..." has been interpreted to encompass nucleic acids that encode amino acids from within the cited fragments. If the claim was intended to be limited to nucleic acids which encode a peptide consisting of the full fragments listed, this rejection can be easily overcome by reciting instead: "a peptide that consists of an amino acid sequence selected from the group consisting of the amino acid [s] sequence at position[s] 1-61 of SEQ ID NO: 6, the amino acid[s] sequence at position[s] 98-111 of SEQ ID NO: 6, and the amino acid[s] sequence at position[s] 161-170 of SEQ ID NO: 6; ..."

12. Claims 1 and 5-7 are rejected under 35 U.S.C. 102(b) as being anticipated by Yang and Kurkinen (J. BC, 1998; vol. 273, pages 17893-17990).

Yang and Kurkinen teach a sequence which comprise *a* sequence set forth in SEQ ID NO 3 and SEQ ID NO: 5 (Fig 1). The sequence of Yang and Kurkinen is identical at positions 183-187 to positions 170-174 of SEQ ID NO 3 and positions 129-133 of SEQ ID NO 5. The claims are not limited to sequences that comprise the [full length] sequence of SEQ ID NOS 5. Yang

and Kurkinen further teach vectors and host cells comprising such sequence (page 17894, col 2 "cDNA Cloning and sequence analysis).

13. NOTE: The amendment to claim 1 necessitated the rejections with regard to claim 1. The rejections in sections 6 and 7 were inadvertently omitted for claims 28 and 29 in the previous office action. These rejection can be overcome by reciting instead "... comprising --the-- [a] nucleotide sequence of SEQ ID NO: 5 (claim 1), or "comprising –the—amino acid sequence set forth in SEQ ID NO: 4 " (or SEQ ID NO: 6, respectively) (claims 28 and 29).

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Brennan in view of Chee (Chee et al; US Patent 5,861,242).

Brennan teaches an array of all possible 10 mer nucleic acids, which would encode fragments of the amino acid sequences listed in claim 3, for use in for example, sequencing by hybridization of a sample containing target nucleic acid (col. 1, lines 15-25, col. 3, lines 10-22, col. 9, line 48-col 10). Brennan does not teach using PCR to amplify the hybridizing sequence (in the sample), however Chee teaches using PCR to amplify target samples prior to analysis with arrays of bound probes (col. 23). Therefore, it would have been prima facie obvious to one

of ordinary skill in the art at the time the invention was made to use PCR in the method of Brennan, to amplify the hybridizing nucleic acid, as taught by Chee. The ordinary artisan would have been motivated to use PCR as taught by Chee because Brennan is silent with regard obtaining the nucleic acid target prior to analysis with the array bound probes, while Chee teaches methods of hybridizing target nucleic acids to arrays and teachings amplifying the target with PCR before array analysis.

Conclusion

16. No claims are allowable.

17. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Sitton whose telephone number is (571) 272-

0752. The examiner can normally be reached Monday-Thursday from 8:00 AM to 5:00 PM and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571) 272-0745. The fax phone number for this Group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Jehanne Sitton

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9/26/05